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10/672,746	09/26/2003	Chao-Wei Liao	U 014824-8	1845

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EXAMINER	
PANDE, SUCHIRA	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 05/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/672,746	LIAO ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☒ Claim(s) 1 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 26 September 2003 is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date [redacted] 12/1/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Drawings

1. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Labels 5 and 8 in Fig 1.; and labels 21, 4; 1, 31; 61, 8 and 5, 71 in Fig 2. are not described in the specification. Fig 7 has a typographical error in Fig legend for lane 2. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

2. The disclosure is objected to because of the following informalities: Page 16, Table I "Codon" in column 2 heading is misspelled. Page 24, line 16 word "series" is misspelled.

Appropriate correction is required.

Internet Address

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in Page 16, line 11. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

4. Claim 1 is objected to because of the following informalities:

Conventionally the ends of primer or DNA are by indicated as the 5' and 3' ends. The prime marks are missing after 5 and 3 end of primer in claim 1.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The description of the forward primers in (i) of step 2 of claim 1 is not consistent with the primer serving to amplify a DNA segment. The part (a1) of forward primer would allow hybridization to 3' end of target sequence. However, the part (b1) located at 3' end of forward primer, that is adjacent to 3'end of part (a1) having homology to 5' end of the template sequence, would not hybridize with the 3' end of target sequence.

This would result in the 3' end of forward primer being unanchored while 5' end of primer is anchored to the template. Such a situation would not allow DNA synthesis to continue in 5' to 3' direction from this primer. It is acceptable in a primer if the 5' end is unanchored but it is absolutely essential that the 3' end of the primer be anchored to the target for DNA synthesis to take place. Identical problem is seen with forward primer (iii) recited in step 2 of claim 1 with parts (a3) and (b3).

The reversed primers of part (ii) recited in step 2 of claim 1 having parts (a2) and (b2) ; and part (iii) recited in step 2 of claim 1 having parts (c3) and (d3) share the exact same problem as described above for forward primers.

Such a two part primer having unanchored sequences at 3' end of primer would not allow DNA synthesis to proceed in 5' to 3' direction.

Claims 2-15 depend on claim 1. Hence all of them are indefinite as described for claim 1 above.

Claim Interpretation

7. All the claims in this application depend on claim 1 and as described above claim 1 is indefinite. For examination purposes, the examiner has interpreted the primers having two parts to be the type of primers that were depicted by applicant in their embodiments illustrated by Fig. 1 and Fig. 2 to analyze the claims. In both these embodiments, the applicant has used two part primers to perform PCR overlap extension protocols where the 3' end of the primer has a region of homology with the target sequence while the 5' end is unanchored.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Horton et. al. (1989) Gene 77:61-68.

Regarding claim 1, Horton et. al. teach:

1) conducting a first polymerase chain reaction on a first template with a first primer pair to obtain a first polymerase chain reaction product. (See Horton et. al. page 63, Fig. 1 Gene I or Gene II);

(2) conducting muti-cyclic polymerase chain reactions by a primer extension technique to obtain a product comprising the target polynucleotide sequence; wherein the template used in each polymerase chain reaction is the product obtained in the previous polymerase chain reaction (see Horton et. al. page 63 legend to Fig 1. lines 7-10).

Horton et. al. teach (see primers c and d in Horton et. al. page 63 Fig 1) primer pairs described in (i) of step 2 of claim 1; the forward primer having two parts (see primer c) and reverse primer d.

Horton et. al. also teach (see primers a and b in Horton et. al. page 63 Fig 1) primer pairs described in (ii) of step 2 of claim 1; the forward primer a and the reverse primer having two parts (see primer b).

Horton et. al. teach primers "d" and "e" in the extension overlap. These primers have a region of 15 nucleotides that allows them to hybridize in the region of overlap. (see page 65, section labeled B: primers). The sequence 5' t gcc gcc cgc gct ct 3' of primer "d" allows it to hybridize to 3' end of exon 2 of H-2K^b and by PCR with primer pair "c" it allows the generation of the fragment to CD. Similarly sequence 5' ggc act cac aca ctc cag 3' of primer "e" allows it to hybridize to 5' end of exon 3 of H-2L^d and by PCR with primer pair "f" it allows the generation of the fragment to EF. 3' end of fragment CD and 5' end of fragment EF share the region of homology overlap provided by primers 'd" and "e" described above. Thereby strand 5' CD 3' can serve as primer for strand 5' EF 3' and allow extension of the fragment CD to form CDEF or conversely strand 5' FE 3' can serve as a primer for strand 5' DC 3' and allow extension of the fragment EF to form fragment 5' CDEF 3'.

Horton et. al. teach use of template in PCR that is the product obtained in the previous PCR. See page 65, section labeled D: PCR products. Here the PCR products fragment "AD" and fragment "EH" serve as templates for the production of recombinant product shown in section E page 65. In this case the 3' end of fragment "AD" shares a region of 15 bp that is homologous to the 5' end of fragment "EH". So the denatured strands of AD and EH can hybridize in the region of overlap to allow for primer extension.

(3) Horton et. al. teaches the technique of overlap extension PCR to obtain the polynucleotide product comprising the target polynucleotide sequence (see Recombinant Product formed in Horton et. al. page 63 Fig. 1 and page 64 Fig. 2 B).

Horton et. al. were interested in creating a chimeric protein containing parts of H2L and H2K so they use these two templates as their starting point (see page 64 Fig. 2.). The example clearly illustrates that the method taught by Horton et. al. can be practiced starting with one single template as envisaged in the present application as the method hinges on the fact that primers have a region of overlap that can be used for extending the PCR product in subsequent cycles.

Horton et. al. make several PCR products that had the overlaps created by the way the primers were designed and extended them in pair wise fashion (see Horton et. al. page 64 Fig. 2 B) by PCR till they got the final product. It should be noted that the same result would have been obtained if they had chosen to first use primers a and b to make fragment AB then decided to extend the sequence by performing PCR after adding primers c and d to the mix. Looking at the sequence of the primers (see Horton et. al. page 65 for listing on primer pairs and the region of homology between them) a, b, c and d in page 65 it is evident that primers b and c share a 15 nucleotide region of complementarity that would allow extension overlap resulting in formation of fragment ABCD during PCR. Since primer e has a region that is complementary to primer d this pair of primers (e and f) would allow fragment ABCD to be extended by extension overlap to create ABCDEF. PCR product ABCDEF in turn would be extended by primers g and h to generate the final product ABCDEFGH. Horton et. al. (See page 63 Fig. 1 legend lines 7-10) explicitly teaches "The intermediates in this reaction are shown in the hatched box. The end of one strand from each product is capable of hybridizing with the complementary end from the other product. The strands having this overlap at

their 3' ends can act as primers for one another and be extended by the polymerase to form the full-length recombinant product". This teaching indicates that Horton et. al. was perfectly aware that primer extension overlap PCR taught by them could also be practiced in the manner of claim 1 using exact same primers.

Regarding claim 2, Horton et. al. teaches removing the first template from the final product by gel electrophoresis. In this case the first templates are H-2L^d and H-2K^b (see page 64 panel A). By performing gel electrophoresis the first templates H-2L^d and H-2K^b get removed from PCR products (the final products) (see page 66, par 2 and Fig. 4).

Regarding claim 3, Horton et. al. teaches restriction sites Sal I and Xho I at both ends of first template (see page 64 H-2k^b template).

Regarding claim 4, Horton et. al. teach primer pairs where fragment that has homology to target polynucleotide in each step is 15 nucleotides. See page 65, Fig. 3, Section C, primer "d" and primer "e" they both share a 15 nucleotide region of homology; and Section D where fragment "AD" and fragment "EH" serve as primers that can be extended by extension overlap here too the region of homology between them is 15 nucleotide. Also see the Fig. 3 legend for Part C and Part D.

Regarding claim 10, Horton et. al. teaches production of a mutant target polynucleotide containing multiple mutations as compared to the starting first templates. (see page 64 Recombinant Molecule formed in Fig. 2 B starting from H-2L^d and H-2K^b). Here the first templates were H-2L^d and H-2K^b and the final target produced by extension overlap is chimeric fusion polynucleotide containing sequences from H-2L^d

and H-2K^b. In this case, the final construct has parts AB and EF that come from H-2L^d while parts CD and GH come from H-2K^b . The intron 2 region of H-2L^d is deleted in the final construct such that exon 2 is directly fused to exon 3. Thus the recombinant target sequence generated contains multiple mutations such as deletions and replacements compared to starting templates.

Regarding claim 11, Horton et. al. teaches primer "a" used to generate fragment AB (see page 64 Fig. 2 top). This primer meets all the criteria recited for helper primer in the claim.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 5-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horton et. al. (1989) Gene 77:61-68 as applied to claims 1 above further in view of Jayaraman et. al. (1991) Proc. Natl. Acad. Sci. 88: 4084-4088, as evidenced by Springer and Sligar (1987) Proc. Natl. Acad. Sci. USA 84: 8961-8965.

A) Regarding claims 5 and 6, Horton et. al. teach the method of synthesizing target nucleotide according to claim 1.

But regarding claim 5 Horton et. al. does not teach changing the codons of the target polynucleotide to codons having high expression efficiency in the host cells.

In addition, regarding claim 6 Horton et. al. does not teach a host that is enteric bacterium.

B.) Regarding claim 5, Jayaraman et. al. teaches changing codons to ensure expression of their gene in *Escherichia coil, Bacillus subtilis* and yeast (see page 4085, par. 6, lines 9-20).

Regarding claim 6, Jayaraman et. al. teaches expression of their gene in variety of hosts including enteric bacterium *Escherichia coil* (see page 4085, par. 6, lines 3-7).

C) Jayaraman et. al. do not provide the minute details for synthesis of a gene coding for isozyme c of horseradish peroxides using extension overlap polymerase chain reaction- mediated gene synthesis but teach that "the gene was also synthesized from its fragments by using an overlap extension method similar to the procedure described by Horton et. al. 1989" (see page 4084 lines 10-13 of abstract).

D) Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use the method taught by Jayaraman et. al. in the method taught by Horton et. al. The motivation to do so is provided by Jayaraman et. al. who state "There appears to be a relationship between expression and the usage of codons in a gene" (see page 4085, par. 6) as evidenced by Springer and Sligar (1987) Proc. Natl. Acad. Sci. USA 84: 8961-8965. Springer and Sligar state "This construction, -------utilized biased *E. coli* codons for highly expressed *E. coli* genes and incorporated an efficient ribosome binding site with optimal spacing 5' to the initiation codon. Total gene synthesis also allowed the incorporation of initiation and termination sequences and convenient restriction-----. This synthesized gene was inserted into the vector puC19 and resulted in the high level production of soluble heme-containing sperm whale Mb in *E. coli.* The expressed Mb constitutes about 10% of total soluble cell protein and is highly stable. We suggest that **the use of preferred codons for highly expressed *E. coli* genes is necessary** for the high-level expression of heme-containing globin in *E. coli.* " (see Springer and Sligar, page 8961 par. 3). In addition they state "we credit the high-level expression of heme-containing globin on the use of preferred codons for highly expressed *E. coli* genes, which reflects the correspondingly larger tRNA pools." (see Springer and Sligar, page 8964 last par. 1st sentence).

12. Claims 7-9 and 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horton et. al. and Jayaraman et. al. as applied to claims 1-6 above, further in view of Baneyx F. (1999) Curr. Opin. Biotechnol. 10(5): 411-421.

A) Horton et. al. teaches the method of producing the target polynucleotide according to claim 1, but ~~neither~~ neither teach transforming a host nor teach expressing the target protein in the transformed host.

B) Regarding claims 7, Jayaraman et. al. teaches a target polynucleotide for expression in transformed host. (see page 4087 par. 3).

Regarding claim 8, Jayaraman et. al. teaches a target polynucleotide for expression in enteric bacterium *E. coli.* (see page 4087 par. 3).

Regarding claim 9, Jayaraman et. al. teaches changing codons (see page 4085, par. 6, lines 13-20).

C) But Jayaraman et. al. do not specifically teach transforming or transfecting the target polynucleotide to the host. They also do not teach a method for expressing the target heterogeneous protein in the transformed or transfected host.

D) Regarding claims 7, 12-15, Baneyx (1999) teaches method for transforming production host and highly expressing a target polypeptide (see page 413, par. 1-3).

Regarding claim 8 Baneyx (1999) teaches enteric bacterium *E. coli* as host (see page 413, par. 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to use method of Baneyx in method of Horton et. al. and Jayaraman et. al with a reasonable expectation of success.

The motivation to do so is provided by the review article of Baneyx who states" Among the many systems available for heterologous protein production, the Gram-negative bacterium *Escherichia coli* remains one of the most attractive because of its

abilities to grow rapidly and at high density on inexpensive substrates, its well characterized genetics and the availability of an increasingly large number of cloning vectors and mutant host strains." (Baneyx page 411, par.1 Introduction).

Conclusion

13. All claims 1-15 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Suchira Pande
Examiner
Art Unit 1637

TERESA STRZELECKA
PATENT EXAMINER
Teresa Strzelecka
4/28/06